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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,806	09/19/2003	Atakan Aydin	4798 US	8736

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 10/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,806	AYDIN, ATAKAN	
	Examiner	Art Unit	
	Christopher M. Babic	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/24/2006*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. 9/15/06
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant's representative pointed the Examiner to where the amended claim was believed to differ from the teachings of Barany. Applicant specifically pointed to claim 1, line 9 originally presented wherein the claim requires that one probe in each probe set further comprise an addressable sequence located between the primer-specific portion and the target portion. The Examiner notified Applicant that Barany would be reviewed to determine if the limitation in question was taught within the reference.

DETAILED ACTION

Status of the Claims

Claims 1-10 are pending. The following Office Action is in response to Applicant's response dated July 24, 2006.

Specification

The objection to the Abstract has been withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Schouten (EP 1 130 113 A1; September 5, 2001).

The following new ground(s) of rejection is made in view of applicable prior are disclosed within the IDS filed July, 24, 2006.

With regard to Claims 1 and 10, Schouten discloses a method for detecting the at least one target nucleic acid sequence in a sample (Figures 2,3; Pages 11-18, for example) comprising a method for detecting at least one target nucleic acid sequence in a sample comprising: forming a ligation reaction composition comprising the sample and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target nucleic acid sequence.

With regard to the phrase, "...and wherein one probe in each probe set further comprises an addressable portion located between the primer-specific portion and the target-specific portion, wherein the addressable portion comprises a sequence," the disclosure of Schouten expressly teaches a "stuffer sequence," (page 11, lines 40-55; page 14, lines 25-45, for example), located between primer-specific portion and the target-specific portion of a probe (page 11, 50-55, for example), can contain a sequence that can be used to discriminate by the use of fluorogenic probes and the 5'nuclease activity of some polymerases (i.e. real time detection) (page 14, lines 25-45, for example).

Thus, if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent

amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values.

With regard to Claims 2-5, Schouten et al. discloses real-time quantitative amplification methods utilizing fluorescent 5' nuclease probes (page 14, lines 25-45, for example).

With regard to Claims 6-9, Schouten et al. discloses real-time quantitative amplification methods utilizing fluorescent hybridization dependent probes (page 14, lines 25-45, for example).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-10 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Barany et al. (U.S. 6,027,889) in view of Godfrey et al. "Quantitative mRNA Expression Analysis from Formalin-Fixed, Paraffin-Embedded Tissues Using 5' Nuclease Transcription-Polymerase Chain Reaction" Journal of Molecular Diagnostics. 2000. Vol. 2, No. 2: Pages 84-91).

With regard to Claims 1 and 10, Barany et al. discloses a method for detecting the at least one target nucleic acid sequence in a sample (Figures 8-17; Columns 9-11; Columns 23-30; Column 41, Example 4, for example) comprising a method for detecting at least one target nucleic acid sequence in a sample comprising: forming a ligation reaction composition comprising the sample and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target nucleic acid sequence, and wherein one probe in each probe set further comprises an addressable portion located between the primer-specific portion and the target-specific portion, wherein the addressable portion comprises a sequence (Figure 24, for example).

Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12; Columns 24,25, for example), however, does not expressly disclose employing real-time detection methods or detection through comparing threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detection of PCR product with dual-labeled fluorogenic oligonucleotide probe (Page 86, Column

1, for example). They further disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

Based on the combined disclosures of the applied references, it would have obvious to one of ordinary skill in the art at the time of invention to modify the ligation dependent reaction/amplification (i.e. LDR/PCR) methods of Barany et al. to incorporate real-time detection methods. It would have been further obvious to one of ordinary skill in the art at the time of invention to detect the presence of a particular nucleic acid sample by comparing threshold values based on signals from fluorescent hybridization dependent probes. A practitioner of ordinary skill in the art would have recognized that if a particular probe set failed to ligate due to a particular nucleotide mismatch (i.e. SNP or allele), it would fail to produce a threshold value in subsequent amplification reactions (and vice versa) thereby allowing one to determine a particular allele at a given locus (i.e. heterozygosity or homozygosity) by comparison of threshold values. At the time of invention, the disclosure of Barany et al. and Godfrey et al. clearly would have provided the instruction and motivation necessary for one of ordinary skill in the art to practice the methods as claimed. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to practice the instant methods as claimed.

With regard to Claims 2-5, Godfrey et al. discloses real-time quantitative amplification methods utilizing fluorescent 5' nuclease probes (Page 86, Column 1, for example).

With regard to Claims 6-9, Godfrey et al. discloses real-time quantitative amplification methods utilizing fluorescent hybridization dependent probes (Page 86, Column 1, for example).

Response to Arguments - Claim Rejections - 35 USC § 103

Applicant's arguments with respect to the previously applied references have been fully considered but they are not persuasive.

Rejection of claim(s) 1-10 over Barany in view of Godfrey

Applicant asserts that neither Barany, nor the combination of references teaches or suggests the features of claim 1. Applicant provides no supporting arguments as to what specific features fail to be taught or suggested by the applied references.

An interview was held with Andrew Finn on September 15 in which Applicant's representative pointed the Examiner to where the amended claim was believed to differ from the teachings of Barany. Applicant specifically pointed to claim 1, line 9 as originally presented wherein the claim requires one probe in each probe set further comprise an addressable sequence located between the primer-specific portion and the target portion. It is submitted that Barany does teach multiple probe sets that have one probe in each probe set further comprise an addressable sequence located between the primer-specific portion and the target portion. It is not that the addressable portion, as defined, is required to be only a sequence located between the primer-specific portion and the target portion. Applicant is directed to figure 24 wherein Barany expressly teaches

multiple probe sets that have one probe in each probe set that further comprises an addressable sequence located between the primer-specific portion and the target portion.

As submitted above, Barany et al. disclose a subsequent amplification step with labeled primers (Figure 11,12; Columns 24,25, for example), however, does not expressly disclose employing real-time detection methods or detection through comparing threshold values.

Godfrey et al. disclose methods for comparing real-time detection values (Abstract; Page 86, Column 2; Page 87, Column 1). They expressly disclose detection of PCR product with dual-labeled fluorogenic oligonucleotide probe (Page 86, Column 1, for example). They further disclose detecting differences in threshold values to quantify the amount of PCR target (Page 86, Column 1, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention to incorporate dual-labeled fluorogenic oligonucleotide probes for detection of the PCR products generated by Barany since Godfrey suggest such a modification for real-time detection of products.

Thus, the rejections are maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that only representative claims will be discussed.

1. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-28 of copending application Andersen et al. (10/665671).

Claim 1 of Andersen et al. recite a method for detecting at least one target nucleic acid sequence in a sample comprising: forming a ligation reaction composition comprising the sample and a ligation probe set for each target

nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion, a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and a first addressable portion located between the 5' primer-specific portion and the target-specific portion, wherein the first addressable portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion, a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, and a second addressable portion located between the 3' primer-specific portion and the target-specific portion, wherein the second addressable portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target nucleic acid sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the first addressable portion, the target-specific portions, the second addressable portion, and the 3' primer-specific portion; forming an amplification reaction composition comprising: the test composition; a polymerase; a first labeled probe, wherein the first labeled probe has a first detectable signal value when it is not hybridized to a complementary sequence, and wherein the first labeled probe comprises the sequence of the first addressable portion or comprises a sequence complementary to the sequence of the first addressable portion; a second labeled probe, wherein the second labeled probe has a first detectable signal value when it is not hybridized to a

complementary sequence, and wherein the second labeled probe comprises the sequence of the second addressable portion or comprises a sequence complementary to the sequence of the second addressable portion; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product; subjecting the amplification reaction composition to at least one amplification reaction; and detecting a second detectable signal value from the first labeled probe and from the second labeled probe at least one of during and after the amplification reaction, wherein a threshold difference between the first detectable signal value and the second detectable signal value of the first labeled probe and a threshold difference between the first detectable signal value and the second detectable signal value of the second labeled probe indicates the presence of the target nucleic acid sequence; and wherein no threshold difference between the first detectable signal value and the second detectable signal value of the first labeled probe and no threshold difference between the first detectable signal value and the second detectable signal value of the second labeled probe indicates the absence of the target nucleic acid sequence.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to the same general inventive concept of detecting a target nucleic acid comprising a ligation

detection reaction further comprising detecting threshold difference of detectable signals.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. Claims 1-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-48 of copending application Friedlander et al. (10/693609).

Friedlander et al. recite a method for detecting the presence or absence of at least one target nucleic acid sequence in a sample comprising: forming a ligation reaction composition comprising the sample, and a ligation probe set for each target nucleic acid sequence, the probe set comprising (a) at least one first probe, comprising a target-specific portion and a 5' primer-specific portion, wherein the 5' primer-specific portion comprises a sequence, and (b) at least one second probe, comprising a target-specific portion and a 3' primer-specific portion, wherein the 3' primer-specific portion comprises a sequence, wherein the probes in each set are suitable for ligation together when hybridized adjacent to one another on a complementary target sequence; forming a test composition by subjecting the ligation reaction composition to at least one cycle of ligation, wherein adjacently hybridizing complementary probes are ligated to one another to form a ligation product comprising the 5' primer-specific portion, the target-specific portions, and the 3' primer-specific portion; forming at least one

amplification reaction composition comprising: at least a portion of the test composition; a polymerase; a double-stranded-dependent specific label, wherein the double-stranded-dependent label has a first detectable signal value when the double-stranded-dependent label is not exposed to double-stranded nucleic acid; and at least one primer set, the primer set comprising (i) at least one first primer comprising the sequence of the 5' primer-specific portion of the ligation product, and (ii) at least one second primer comprising a sequence complementary to the sequence of the 3' primer-specific portion of the ligation product; subjecting the at least one amplification reaction composition to at least one amplification reaction; and detecting a second detectable signal value at least one of during and after the at least one amplification reaction, wherein a threshold difference between the first detectable signal value and the second detectable signal value indicates the presence of the target nucleic acid sequence, and wherein no threshold difference between the first detectable signal value and the second detectable signal value indicates the absence of the target nucleic acid sequence.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to the same general inventive concept of detecting a target nucleic acid comprising a ligation detection reaction further comprising detecting threshold difference of detectable signals.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-10 are rejected. No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on July 24, 2006 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

10/6/06

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10/12/06